REMARKS/ARGUMENTS

After entry of this amendment, claims 33-34 and 56-67 are pending. Claims 1-32 and 35-55 have been canceled, and new claims 56-67 have been added.

The brief description of the drawings section of the specification has been amended to recite a brief description of Figs. 15A, 15B, 15C, 15D, and 15E. The specification has also been amended to conform to five of the replacement drawing sheets submitted herewith, *i.e.*, Fig. 15A, Fig. 15B, Fig. 15C, Fig. 15D, and Fig. 15E, respectively. The paragraph beginning on page 5, line 20, has been replaced with six replacement paragraphs. The replacement paragraphs describe Figures 15A-15E, 15A, 15B, 15C, 15D, and 15E, respectively. The paragraph beginning on page 69, line 1 has also been amended to identify Figures 15A-15E.

The paragraphs beginning on page 65, line18, and page 77, line 3, have been amended to conform the alum concentration to the alum concentration recited in Figure 15 as filed in U.S. Application No. 09/201,430, filed November 30, 1998. The instant application claims priority to U.S. Application No. 09/201,430.

Support for the claim amendments and new claims is found throughout the specification. Support for an antibody binding to an epitope within residues 1-10 of Aβ is provided at *e.g.*, p. 3, line 2. Support for a chimeric, human or humanized antibody is provided at *e.g.*, pp. 16-21. Support for a single-chain antibody is provided at *e.g.*, p. 21, lines 23-24, and support for an antibody of IgG1 isotype is provided at *e.g.*, p. 21, line 19. Support for expression in blood cells is provided at *e.g.*, p. 25, line 10. Support for immunoglobulin or CMV promoter and enhancer elements is provided at *e.g.*, p. 25, lines 10-13. Support for polynucleotides encoding antibody chains in the same vector is provided at *e.g.*, p. 25, line 15. Support for humanized 10D5 or humanized or human antibodies with the same binding specificity as 10D5 is provided at *e.g.*, p. 57 (10D5 antibody), p. 16, line 29 (humanized antibodies with same binding specificity, and p. 18, line 10 (human antibodies with same binding specificity). Support for a constant region responsible for effector function is provided at *e.g.*, p. 15, line 13. Support for a dosage of at least 10^9 virions is provided at *e.g.*, p. 29, line 3. Applicant responds to the Examiner's comments using the paragraph numbering of the office action. No amendment should be viewed as an acquiescence in any ground of rejection.

3. The cross reference to related applications section has been replaced with a replacement paragraph which recites the domestic priority claim for the instant case, and a supplemental ADS which also recites the domestic priority claim is submitted herewith. Thus, the specific reference requirement of 35 U.S.C. § 119(e) and § 120 is satisfied.

4. Drawings

Amendments to Figure 11

As requested by the Examiner, Figure 11 has been amended to add a legend. Support for this amendment can be found at page 52, lines 3-12.

Amendments to Figures 15A-15E

As requested by the Examiner, the brief description of the drawings section of the specification has been amended to recite a brief description of Figs. 15A, 15B, 15C, 15D, and 15E.

Figures 15A-15E have been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Figure 15D as filed in the instant application discloses an alum concentration of 2 μg/ml. Amended Figure 15D discloses an alum concentration of 2 mg/ml. Support for both of these amendments is provided by the informal Figure 15 as originally filed in the parent application. Thus, the amendments to the Figs. 15A-E contain no new matter.

Amendments to Figure 16

The descriptive term "Anti AB" has been replaced with the term "Anti-Abeta" to give greater clarity to the title. The sentence beginning on page 78, line 33 of the specification.

5. Information disclosure statement.

Applicants' citation of the references has included all the elements required to comply with 37 C.F.R. §§ 1.97-98 that are known to them.

6-7. Claims 33-34 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description due to failure to disclose sequences of antibodies or nucleic acid encoding the same. Applicant previously pointed out that the case law cited in the last office action was directed to either issues of new matter (*see Vas Cath*) or *de novo* isolation a nucleic acid encoding a particular protein, such as human EPO or FGF (*see Fiers, Amgen,* and *Fiddes*), neither of which is at issue here. Applicant also pointed out that the PTO Guidelines for applying the written description requirement recognize that antibodies can be described by reference to the antigen to which they bind without amino acid sequence information due to the mature state of the art and conserved features of antibody structure. The Examiner now responds that the present claims are directed to nucleic acids encoding antibodies rather than antibodies per se, and it is not possible to predict the sequence of a nucleic acid from the antigen to which it binds. The Examiner also alleges that the specification lacks written description of nucleic acids encoding antibodies capable of plaque removal in view of the specification's alleged teaching that only certain antibodies are effective for this purpose. Applicant respectfully traverses.

The logic supporting definition of classes of antibodies in functional terms also applies to defining nucleic acids encoding the antibodies in similar functional terms (*i.e.*, by reference to the antigen that is bound by the class of antibodies). The logic for antibodies per se is based on the fact that although antibodies constitute a large and diverse population as a whole, the members within have common recognizable structural domains (*e.g.*, constant regions, variable region frameworks, and CDRs). Nucleic acids encoding antibodies have analogous structural features. Such nucleic acids are formed by rearrangement of component genes. Light chains are formed by rearrangement of C-regions, V-regions, and J regions, and heavy chains by rearrangement of C-regions, V-regions, J-regions and D-regions. Although the number of different permutations resulting from different rearrangements of these components is very large, the numbers of different types of each of the component genes in a given organism are far from infinite, and many of these component genes have been sequenced. For example, there are nine

constant region genes, six J region genes, and at least 100 variable region genes are available for forming heavy chain genes. (*See* Sites *et al.*, *Basic & Clinical Immunology* (Appleton & Lange, 1994) at p. 81., attached hereto). The nucleic acids encoding antibodies can thus be viewed as different permutations of a common source of building blocks of known sequence. Therefore, like antibodies, nucleic acids encoding antibodies have common recognizable structural features.

The Examiner's position that nucleic acids encoding antibodies are different from antibodies in terms of written description is based in part on the fact that one cannot predict the sequence of a nucleic acid simply from knowledge of the antigen to which the antibody encoded by the nucleic acid bind. However, the unpredictability of sequences is equally applicable to both amino acid sequences of an antibody and the nucleic acid sequence encoding the antibody. One cannot predict the amino acid sequence of an antibody that binds to an antigen simply from knowledge of the antigen any more than one can predict the nucleic acid sequence of the nucleic acid encoding the antibody. Thus, predictability of primary sequence does not provide a basis for distinguishing between requirements for written description of antibodies and nucleic acids encoding antibodies.

Alleged difficulties in identifying which antibodies are effective in removing amyloid deposits also do not provide a basis for distinguishing antibodies and the nucleic acids encoding them in terms of the requirement for written description of nucleic acids. Assuming arguendo that a subclass of antibodies is effective in removing amyloid deposits, this class of antibodies can be characterized by defining the epitope location to which the antibodies bind. This information sufficiently characterizes an antibody subclass in that knowing this parameter and given the mature state of the art, one can readily produce exemplary antibodies having the requisite epitope specificity. Similarly, given the same information and mature state of the art, one can readily produce nucleic acids encoding antibodies having a desired epitope binding specificity using, *e.g.*, the phage display technique (*see, e.g.* , U.S. 6,057,098, attached hereto). The nucleic acids are cloned into a phage display vector, phage displaying antibodies are screened for binding to the desired epitope, and nucleic acids encoding antibodies are isolated from binding phage. These nucleic acids are then expressed to produce antibodies. Accordingly, in such methods nucleic acids encoding antibodies are isolated before the antibodies. Given that antibodies having a given epitope specificity and the nucleic acids encoding them can both be

routinely isolated, and that in some methods, nucleic acids are in fact isolated first, it would be anomalous to hold that antibodies can be appropriately characterized by a binding specificity whereas nucleic acids encoding them cannot.

The Examiner has not addressed the distinctions over the cited case law discussed in the previous response. To reiterate, the *Vas-Cath* case arose in the typical context of determining new matter. Specifically, the issue was whether drawings of a catheter in a design application provided written description of claims that appeared in a utility application claiming priority to the design application. However, here the Examiner's rejection is applied to originally filed claims and no issue of new matter has been raised.[1] *Vas-Cath* does not address what written description is required for originally filed claims.

The *Fiers*, *Amgen* and *Fiddes* cases address written description in situations in which the invention lies in cloning a nucleic acid encoding a particular protein, such as human EPO or FGF for the first time. In circumstances in which the invention lies in cloning a gene, it is perhaps not unreasonable that a newly isolated gene cannot be described without determining its sequence. By contrast, in the present claims, the invention lies not in the de novo isolation of a new gene, such as EPO, but rather in the use of nucleic acids encoding a class of antibodies to a particular defined region containing an epitope of a well characterized antigen (Aβ) for a particular purpose (*i.e.*, treating an amyloidogenic disease characterized by deposits of Aβ). There is no case law holding that a population of nucleic acids encoding a population of antibodies requires sequence data to satisfy the written description requirement. For the reasons outlined above, it is submitted that nucleic acids encoding antibodies should be treated the same way as antibodies themselves in terms of the written description requirement. Thus, provision of sequence data should not be required for nucleic acids encoding populations of antibodies any more than for populations of antibodies per se.

For these reasons, withdrawal of the rejection is respectfully requested.

[1] The claims have been amended. However, the rejection as phrased in the office action was directed to the original claims.

8. Claims 33-34 stand rejected under 35 U.S.C. § 112 for alleged lack of enablement. The Examiner cites Peterson as discussing difficulties in folding of antibodies in bacteria. The Examiner alleges that such difficulties may also be experienced in patients because only B-cells are known to express immunoglobulins and the expression systems described in the specification do not appear to target expression of nucleic acids to B-cells. The Examiner also alleges the specification fails to identify particular nucleic acids encoding clinically relevant antibodies. The Examiner alleges that the specification shows that only certain antibodies were effective in clearing amyloid deposits. The Examiner also alleges that the claims encompass prevention or treatment of any disease associated with amyloid deposit including diseases such as amyloid angiopathy of the vascular or immune systems. The Examiner also alleges that the specification fails to show that treatment results in amelioration by a symptomatic measure. Applicant traverses, addressing the Examiner's points in turn.

With respect to the alleged difficulties in appropriately expressing antibodies in patients, applicant notes that such has been successfully achieved using adenoviral delivery. (*See* Arafat *et al.*, *Gene Therapy,* 9, 256-62 (2002), attached hereto). Adenoviral delivery is a standard method of gene therapy, and is disclosed in the present specification as a means of delivery (*see* specification at p. 25, line 17). Applicant also notes that antibodies have been expressed in eukaryotic cells that do not naturally produce antibodies (*e.g.*, plant and insect cells). (*See, e.g.*, Schillberg *et al.*, *Cell. Mol. Life Sci,*. 60(3), 433-45 (2003) (expression of antibodies in plants), and Guttieri *et al.*, *J. Immunol. Methods*, 246, 97-108 (2000) (expression of antibodies in insect cells), abstracts attached hereto). Thus, it cannot be reasonably be assumed that certain difficulties that may have been encountered in folding antibodies in bacteria would also occur in eukaryotic cells in a patient.

With respect to identification of antibodies capable of clearing amyloid deposits, the claims have been amended to specify that the antibodies bind to an epitope within Aβ1-10. The present specification provides evidence that one such antibody 10D5[2] is particularly effective in clearing deposits (*see* p. 75, lines 9-10). Evidence that additional antibodies binding within Aβ1-10 are effective is provided in a related application, published as WO 00/72880 at p.

[2] Although the present application indicates the epitope specificity of 10D5 as being within Aβ1-16, this has been refined to being within Aβ3-6 (*see* WO 00/72880 at p. 97).

97. Given the identification of the epitope to which a desired class of antibody binds, that epitope occurs within a well characterized antigen, *i.e.*, Aβ, and the mature state of the art, it would have been a routine matter to have produced any number of antibodies binding to such an epitope and nucleic acids encoding the same.

With respect to the allegation that the claims encompass treating all diseases characterized by amyloid deposits, it is noted the claims as amended refer to diseases characterized by amyloid plaques comprising Aβ. Such plaques constitute the pathology found in Alzheimer's disease, and are also known to be present in Down's syndrome (*see, e.g.*, Glenner *et al.*, *Biochem. Biophys. Res. Comm.*, 122, 1131-1135 (1984))[3]. However, the amyloid deposits in vascular amyloidosis are not organized into plaques. The evidence discussed below indicates that amyloid plaques characteristic of Alzheimer's disease can be cleared by antibodies, and that such clearing results in symptomatic improvements. It is therefore reasonably expected that in other diseases characterized by similar pathology (*i.e.*, amyloid plaques comprising Aβ), treatment with antibodies would result in a clearing of that pathology, resulting in a similar beneficial effect resulting from an amelioration of the clinical symptoms.

Although the Examiner reiterates remarks from the previous office action regarding alleged lack of symptomatic measurements in the present specification, she does not address the Janus and Morgan references[4] which show improved cognitive effects in transgenic mouse models treated vaccinated with Aβ. Further, symptomatic analysis of patients in a phase I human clinical trial and postmortem analysis of patient in a phase II human clinical trial support the position that clearance of Aβ in the brains of transgenic mice is a valid predictor of clinical benefit in humans. Data from the phase I human clinical trial showing cognitive effects is described in the attached declaration by Dr. Martin Koller.[5] The declaration describes a phase I trial in which Aβ42 (42 amino acid form of Aβ, a.k.a. AN1792) plus the adjuvant QS-21 was administered to patients suffering with Alzheimer's disease in comparison to a placebo control group (adjuvant alone). The functional disability of patients in this trial was assessed before treatment with Aβ commenced (baseline) and at intervals thereafter. The clinical outcome

[3] Glenner *et al.* was cited by the supplemental IDS submitted October 9, 2001 as cite no. 114.
[4] The Janus and Morgan references were attached to the response filed September 26, 2003.
[5] The declaration of Martin Koller was first submitted on May 27, 2003 in a related case, U.S. Application No. 09/724,953 filed November 28, 2000.

measure used to measure functional disability was the Disability Assessment for Dementia (DAD) scale. The average DAD score of patients administered placebo declined by 31.38 points from the baseline to final visit. (*See* Table 1 of the Declaration of Martin Koller.) The decline in score indicates a decline of functional abilities of the patients. The decline of average DAD score of patients administered AN1792/QS-21 was inhibited in each of the three treatment groups. Dr. Koller concludes that the results from the clinical trial provide statistically significant evidence that administration of AN1792(QS-21) to humans is beneficial in treating Alzheimer's disease.

Data from a postmortem analysis of a patient participating in a phase II human clinical trial is described by Nicoll *et al.* (*see* Nicoll *et al.*, *Nature Medicine*, 9(4):448-452 (April 2003))[6]. After the phase II trial was halted, a woman died from causes unrelated to the trial and her brain was subject to a postmortem analysis. The analysis showed three major features in common between the brain from the treated human and the brain of a treated PDAPP mouse. First, there were extensive areas with a low-density of Aβ plaques without plaque associated dystrophic neurites and GFAP-immunoreactive astrocytes. Second, Aβ immunoreactivity was associated with microglia in areas devoid of plaques. Third, there was persistence of cerebrovascular amyloid. (*See* the first column, last paragraph of p. 4.) Thus, the Nicoll paper shows many similarities between treatment of Alzheimer's disease in humans and the PDAPP mouse including "therapeutic modification of the neuropathology of AD with removal of Aβ from the human brain." (*See* p. 4, second column, first paragraph.)

For these reasons, withdrawal of the rejection is respectfully requested.

[6] Nicoll *et al.* is cited as cite no. 350 on the PTO/SB/08B form attached to the supplemental IDS submitted herewith.

9-10. Claim 33 has been amended as suggested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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